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14. ABSTRACT

This program is intended to establish the infrastructure to provide state-of-the art targeted radiation therapy to military personnel and veterans with cancer. The research aspect of this project is intended to demonstrate whether 1) targeted radiation therapy with real time localization and tracking will allow use of a smaller planning treatment volume margin with a significant decrease in rectal and bladder volume treated and whether the use of such targeted therapy can occur within standard treatment times and thus feasible for routine clinical use, 2) whether the use of Vac-Lok® immobilization devices are necessary when patients are treated using the Calypso system, 3) whether Beacon® Transponder is of benefit in pelvic radiation therapy following prostatectomy, 4) whether hypofractionated treatment plans which are more beam on time per fraction which may potentially account for more intra-fraction organ movement but allow for a shorter duration of treatment are feasible for routine clinical use with the Calypso system and 5) whether use of the Calypso system, and other advanced radiation therapy equipment, can improve treatment techniques and outcomes in malignancies arising in other parts of the body.

15. SUBJECT TERMS
Calypso, Prostate, Intensity Modulated Radiation Therapy (IMRT), Planning Target Volume (PTV), Beacon Transponders

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Targeted Radiation Therapy for Cancer Initiative Annual Report

Introduction:

The full potential of radiation therapy has not been realized due to the inability to locate and track the tumor target continuously during the delivery of the radiation dose. Without the ability to accurately locate the tumor target at the time of dose delivery, more of the patient's healthy tissue is exposed to radiation, which may result in acute or chronic complications. The research studies and activities described in this report will improve the techniques of modern radiation therapy and directly benefit the Departments of Defense by: providing improved, state-of-the-art prostate cancer treatments to active-duty military personnel and veterans; continuing to investigate reduction of the number of daily radiation treatments required for each patient thereby reducing the cost of care and increasing treatment capacity within the military delivery system; enabling research to establish standards of care for targeted radiation therapy; establishing a DOD center of excellence in targeted radiation therapy and accelerating the development of the targeted radiation therapy platform to treat additional cancers that significantly affect service personnel, their families, and veterans, such as breast cancer and metastatic cancer. The Calypso® 4D Localization System is a FDA Class II device, utilized to track both inter-fraction and intra-fraction tumor movement in patients receiving radiation therapy for various malignancies.

Body: <u>Task Completion</u>

Task 1. *Establishment of centers for targeted radiation therapy at MAMC and VAPSHCS with installation of the Calypso® 4D Localization System.*

Installation of the Calypso® 4D Localization System occurred at MAMC. The radiation team continues to receive training and technical support of the system from Calypso as needed.

The installation and training of the Calypso System also occurred at VAPSHCS. No study patients were ever treated at the site. The system was de-installed and moved to MAMC to be used in the newly renovated second vault with the new linear accelerator.

Task 2. *Treatment for prostate cancer with state-of-the art technology to allow real-time localization and continuous tracking of the tumor target.*

A total of 23 non-study prostate cancer patients who did not otherwise qualify for a protocol have been treated with the Calypso system at MAMC. Non-protocol patients have allowed the providers to gain further proficiency with the Calypso unit. Six of these patients have been treated in the prone position. The experience and knowledge gained in this alternative positioning technique has allowed for patients who were not anatomically compatible with the Calypso system in the supine position to be able to

receive treatment with this state-of-the-art localizing/tracking device. The Reduced Margins protocol was amended to allow for prone positioning and thus far we have treated 2 study patients in this position.

MAMC has now been routinely using the newly approved FDA surface transponders off protocol to monitor breathing motion during our standard breath-hold technique for treating left-sided breast cancer, which allows sparing of the heart. We have thus far treated 23 patients using these approved external beacons. The Calypso system provides a previously unavailable level of additional positional monitoring for these patients and we have gained considerable expertise with this technique. We submitted and received approval for a retrospective breast cancer protocol and are awaiting final approval from HRPO. This research study will evaluate the benefits of this breath-hold technique, including quantifying dose reduction to the heart. Our goal is to write a paper for publication and possibly present the results at a professional conference. We anticipate opening a breast cancer protocol in the near future which will prospectively evaluate the benefits of this technique, including quantifying dose reduction to the heart. An amendment was made to the current SOW to include this new protocol. See Task 8 for further details on this protocol.

Task 3. *Feasibility study with reduced planning treatment volume (PTV) margins and intensity modulated radiation therapy (IMRT) using targeted radiation therapy.*

Twenty Four subjects have been consented and twenty two enrolled in the study with Reduced PTV Margins at MAMC to date. Eleven of these subjects have completed the trial and ten are in the follow-up phase, one is still undergoing treatment and two were screen failures that never started treatment.

Amendments, reviews and deviations that have occurred and been reviewed by the MAMC IRB in the last year include: 1.Removed VAPSHCS as a study site. 2. Clarifications were made to the study visit descriptions in the informed consent. 3. Brooke Army Medical Center (BAMC) was added as a site (approval by MAMC IRB was granted, however, BAMC IRB is still processing the regulatory documents). 4. MAJ Brownwyn Stall from BAMC was added as a Sub-Investigator. 5. Continuing review was approved by the MAMC IRB (submitted for review at HRPO) from 18 July 2013 through 17 July 2014. All potential patients that are seen at the weekly multidisciplinary prostate cancer clinic and or by provider referral are being considered for participation and are given the option to partake.

We recently presented a poster presentation based on the association of anorectal angle with bowel toxicity of the first 10 study patients from The Reduced PTV Margins study. The first author, CPT Marisa Gosswiler , radiology resident at MAMC, presented the poster at the Cancer Imaging and Radiation Therapy Symposium in Orlando, Florida (February 8-9, 2013). CPT Gosswiler also presented this data at Madigan's Research Day on April 26th. We have now presented two presentations at a national conference and one here at Madigan supported by the data collected from this trial. We hope to continue our momentum and enroll new patients on this study for another year which

includes a 2 year follow-up to assess for toxicity after treatment ends. A two-year no-cost extension will be necessary to make this possible. If not, we will have to amend the current protocol to end enrollment and shorten our follow-up period to one year.

VAPSHCS received full regulatory approval, but never consented any subjects. This site is now closed.

In an effort to boost enrollment, we have collaborated with Brooke Army Medical Center. BAMC is currently treating patients using the Calypso system (non-protocol patients not under this grant) and has an abundant subject population that meets the protocol requirements. MAMC IRB has given their approval and we are now waiting for BAMC to process the regulatory review on their end. Once BAMC IRB approval is granted we will submit to HRPO for review. MAMC will remain the board of record for this protocol at both sites.

This study is expected to enroll a combined total of up to 40 subjects from both centers.

Task 4. *Hypofractionated Radiotherapy in Patients with Favorable Risk Prostate Cancer Using the Calypso® 4D Localization System.* .

The original hypofractionated trial listed under this task has been removed and replaced with this Radiation Therapy Oncology Group (RTOG) study. The SOW was amended to include this change.

We are enthusiastic to partake in the RTOG 0938 phase II randomized multicenter trial to assess acute and late toxicity for two different hypofractionated regimens. Our participation will allow us to contribute our expertise with the Calypso system since to our knowledge few, if any, other centers participating in this study have used Calypso localization for treating study patients.

Participation in RTOG 0938 will allow us to help answer an important research question being addressed at the national level, and we will be able to contribute our expertise with Calypso localization in this setting. Our participation will also contribute significantly towards the overarching goal of establishing a center of excellence for cancer radiation therapy.

We submitted an application to become an affiliate RTOG member and it is currently under review for acceptance. Dr. Christopher Jones, PI at Radiological Associates of Sacramento agreed to sponsor us as the 'parent site' (RTOG affiliate membership requirement). The Radiation Therapy Oncology Group is a recognized leader in working to increase survival and improve the quality of life for cancer patients. Becoming an affiliate member of RTOG will open many research doors within our military setting and allow us to offer our patients the decision to participate in the most up-to-date radiation therapy techniques available.

As soon as we receive membership approval, we will submit the 0938 study for MAMC and HRPO regulatory approval.

Task 5. *A Randomized Study Comparing External Pelvic Immobilization to Limited Immobilization for the Treatment of Prostate Cancer with IMRT Using Real-Time, State -of-the-Art Motion Tracking with the Calypso® 4D Localization System.*

Eight subjects have been enrolled in the Immobilization study at MAMC to date. A total of eleven signed consent; three were screen failures and never started treatment. All eight of these subjects have completed the study from consent to the one year follow-up. We continue to actively pre-screen all potential subjects and offer them participation in the trial.

As stated in Task 2, we continue to develop expertise in using the alternative prone positioning for treating patients who are too anatomically large to be compatible with the Calypso System in the standard supine position. As we gain more knowledge from the data collected from the prone patients on the Reduced PTV Margins study, we will consider amending this protocol to allow the high-risk stratification sub-set also to be treated in this prone treatment position.

We submitted an abstract to a professional conference, but were not chosen to present due to our limited data at the time. We hope to resubmit an abstract based on intra-fraction prostate motion and total treatment time for a future conference once we have compiled more data.

No amendments or deviations occurred in the last year. The continuing review is scheduled to occur on 27 August 2013. The current review approval period is from 29 August 2012 through 28 August 2013.

VAPSHCS received partial regulatory approval. No subjects were ever consented. This site is now closed.

This study has proven to be difficult to enroll since most patients who are intermediate to high-risk choose to have a prostatectomy. Our original goal of 20 subjects does not seem feasible at this time. A more attainable goal that would still allow us to gather enough data to support our study endpoints would be to enroll 10-15 subjects.

Task 6. *Post-prostatectomy Daily Target Guided Radiotherapy Using Real-Time, State-of-the-Art Motion Tracking with the Calypso® 4D Localization System: A Feasibility Study.*

Sixteen subjects have been enrolled in the Immobilization study at MAMC to date. A total of twenty have signed consent; four were screen failures and never started treatment. Ten of these subjects have completed the study, five are in the follow-up phase and one is undergoing treatment

Amendments, reviews and deviations that have occurred and been reviewed by the MAMC IRB in the last year include: 1. Deviation that was acknowledged by MAMC IRB: Per the protocol, all patients with a detectable PSA (defined as $\geq$ 0.1 ng/dl) will have a total body scan and CT scan of the pelvis before treatment; subject #3010 had a PSA of 0.13 ng/dl but did not have imaging. It was noted in the patient's records that CT abd/pelvis or bone scan would not add anything to this patient's work-up as the patient had moderately differentiated prostate cancer and his absolute PSA level was very small making the pre-test probability of either of these studies being truly positive was very small. In the future if a deviation is being considered due to clinical relevance, a protocol exception request will be sent to the IRB for review prior to the occurrence. 2. The current review approval period is from 24 October 2012 through 23 October 2013.

We presented a poster presentation based on quantitative analysis of the cone-beam CT scan data collected on the first 10 patients of this clinical trial. The first author, CPT Madeera Kathpal, visiting from Fort Sam Houston resident unit, presented the poster at the 2013 Genitourinary Cancers Symposium in Orlando, Florida (February 14-16, 2013) CPT Kathpal also presented this data at Madigan's Research Day on April 26th. We have also been selected to present 2 more poster presentations supported by the data collected from this trial at the ASTRO 2013 Annual Meeting being held on September 22-25 in Atlanta, Georgia, USA. The first is titled, "Differences Between Beacon-Localized and Cone-Beam CT (CBCT)-Localized Radiation Therapy to the Prostatic Fossa" and "Inter-Fraction Displacement of Electromagnetic Beacons in Patients Receiving Post-Prostatectomy Radiation Therapy". As the first author, CPT Kathpal will attend this conference and present the posters.

The data gathered from this process will enable us to determine how much we can safely reduce the PTV margins for a follow-on reduced PTV margins study. The localization data captured from this protocol and from any future follow-on reduced PTV margins protocol will eventually be analyzed in aggregate to provide the best possible data on localizing the prostatic fossa using Calypso beacons. The SOW was amended to include this study (see task 6a below)

VAPSHCS received partial regulatory approval. No subjects were ever consented. This site is now closed.

This study is expected to enroll 20 subjects.

Task 6a. *Reduced PTV Margins Post-prostatectomy Daily Target Guided Radiotherapy Using Real-Time, State of-the-Art Motion Tracking with the Calypso® 4D Localization System: A Feasibility*

The quantitative analysis of the cone-beam CT scan data collected from the original protocol outlined in Task 6 will determine how much of the PTV margins can safely be reduced. To date, we have determined that using Calypso beacons for localization will

allow us to safely spare approximately 1 cm of normal bladder, which is included in the clinical target volume (CTV) when treatments are localized with other techniques.

Our analysis to date of the CBCT data collected in Task 6 demonstrates that most patients would be appropriately treated with significantly decreased circumferential margins; however a few patients are outliers who require more margins. It has been demonstrated by other groups that these outliers can be identified by analysis of target volume coverage during the first five treatments, followed by margin adaptation based on this analysis. Therefore, this protocol will also include an adaptive radiation therapy component, by which each patient's first five fractions of radiation therapy will be analyzed for a pattern of excessive target volume motion, and margin adjustments will then be made to the patient's radiation treatment plan if necessary.

We anticipate starting this study in the next few months.

Task 7. *Phase I/II trial of Real Time targeting of metastatic lesions in the liver with hypofractionated radiation therapy.*

We will not be pursuing this liver cancer protocol since the Calypso System is still not FDA approved for this indication. Instead, we have amended the SOW to replace this task with the following:

Central Dose Escalated Palliative Conformal Radiation Therapy

This study will include two phases and has the potential to dramatically alter the efficiency and efficacy of palliative radiation therapy. The primary goal of this study is to develop and validate a set of dosing guidelines that will allow widespread use of advanced technology radiation therapy techniques, such as IMRT and VMAT, in treating palliative patients. The main obstacle to overcome in reaching this goal is to establish practice patterns that allow simplified, though still safe, use of this technology in order to decrease the expense associated with these treatments. Currently, palliative patients with a single, or very few metastases, may be referred for stereotactic body radiation therapy, a time-consuming, expensive, and not widely applicable therapy. The other option for palliative patients tends to be simple 2-D or 3-D planned treatments which are not particularly conformal and are usually delivered over 10 fractions. Our study will seek to demonstrate the practicality of a middle ground between these two techniques – on the one hand bringing the benefits of intensity modulated dose escalation to palliative patients, but on the other hand maintaining simplicity, efficiency, and widespread applicability of treatment.

We anticipate starting this study in the next few months.

Task 8. *A Retrospective Study of Breast and Chest Wall Positioning During Whole Breast Radiation Therapy for Left-Sided Breast Cancer Using Breath-Hold Technique Supplemented by Motion Tracking with the Calypso® 4D Localization System.*

This study will examine the precision and accuracy of radiation therapy using breath-hold technique for left-sided breast cancer patients treated with adjuvant radiation therapy, with the benefit of confirmatory tracking via the Calypso® 4D Localization System.

Approximately 15 left-sided breast cancer patients who were treated using FDA approved surface beacon transponders to monitor respiratory motion will be evaluated.

We will quantify dose reduction to the heart with this technique. We will also quantify the ability of surface transponder beacons to accurately track chest wall motion in general, and evaluate potential for electromagnetic surface transponders to allow a decrease in normal tissue margins used when planning breast and breast boost fields.

Our hypothesis is that this technique will demonstrate accuracy and precision that is well within the traditional 1 cm margin of error, allowing a potential decrease in planning margins.

We have received MAMC IRB approval and will begin consenting patients as soon as we get approval from HRPO. We anticipate opening a prospective study based on data analysis of this trial.

Task 9: *Establish a center of excellence for targeted radiation therapy. The intent of this task is to create a facility specialized in all modalities of targeted radiation therapy such as cone beam CT, on board kilovoltage orthogonal imaging, and the Calypso® 4D Localization System*

The staff at MAMC have treated close to 100 patients with the Calypso® 4D Localization System and continue to develop expertise as a center of excellence in targeted radiation therapy. This grant continues to facilitate continuing medical education for the staff at MAMC on image guided radiotherapy. Additional education materials and visits from other DOD providers will be coordinated in upcoming years of the project.

An active duty Army Radiation Oncologist resident, Madeera Kathpal has now completed two rotations at MAMC during the months of September and January/February. The resident learned advanced techniques of tumor targeting with the Calypso system and assisted in evaluating data and writing scientific papers under the guidance of the MAMC physicians. One of the projects she worked on was completing/submitting an abstract to the 2013 Genitourinary Cancers Symposium. The abstract is based on data collected from the Post-Prostatectomy study. She presented this data at the Genitourinary Symposium mentioned in February via a poster presentation. She presented an oral presentation of this data at Madigan's Research Day in April. She also developed a rough draft manuscript on one of the next protocols we anticipate opening at MAMC; our retrospective analysis of our use of surface beacon transponders with the Calypso System to monitor breathing motion in left-sided breast cancer patients in an effort to reduce late radiation side effects. This protocol was further developed and submitted to the MAMC IRB. Dr. Kathpal has helped the team tremendously in our

research endeavors. We are fortunate to have her return at the end of August for her 3rd rotation.

We have also had a MAMC Radiology resident and two medical students on research rotations assist in evaluating, preparing and writing abstracts based on the data gathered in our Reduced PTV Margins and Immobilization protocols. CPT Gossweiler, radiology resident, has presented a poster presentation at the Cancer Imaging and Radiation Therapy Symposium in Orlando, Florida (February 8-9, 2013). She was selected and presented an oral presentation at Madigan's Research Day in April. Her next project will be to assist in the analyzing of the retrospective breast cancer protocol.

We have now hosted four educational conferences/visiting professorships in the area of urology and radiation oncology since the inception of this grant. We have committed to making these events an annual occurrence. We believe these educational events promote our site as a "center of excellence in target radiation therapy" and encourage physicians in the community to seek our expertise. Our most recent event was held on 09 August 2013. Dr. Ruth Etzioni, PhD, an epidemiologist at Fred Hutchinson Cancer Research Center in Seattle spoke on the topic of screening for prostate cancer. As expected, this year's symposium had the largest attendance to date due to the very high interest by the medical community regarding this topic. We received positive feedback from many of the providers. We look forward to hosting the 5th annual symposium next year.

We continue to collect information regarding problems/challenges encountered with Calypso as a "Lessons Learned Log" which identifies the problems encountered with possible causes and the techniques used to solve the problem. The physicist at our site has been asked to speak about using the Calypso System at a professional physics conference in October. She plans to incorporate some of our "lessons learned" information in her speech.

Task 10: *Present findings of feasibility studies at professional conference.*

We have presented a total of 3 poster presentations at 2 prominent medical symposiums based on the continued findings of the Reduced PTV Margins feasibility study and the Post-Prostatectomy protocol. We have been selected to present 2 more in September 2013. This will mark a total of 5 presentations at a professional conference. Also mentioned prior in this report, we have presented 2 presentation at Madigan research day. We hope to have the opportunity to present many more in the years to come.

Problem Areas:

As previously reported, it was unanimously decided to discontinue efforts at VAPSHCS based on several factors which included: radiation therapy staffing issues at the VA, the slow pace of the VA IRB system, and most fundamentally the practice pattern of the Seattle VA which focuses on brachytherapy as treatment for prostate cancer. It seemed unlikely that patient accrual would substantially contribute to our research. The SOW was updated to remove the VA.

The Calypso System at the VA was de-installed and moved to MAMC to be used with our newly installed treatment machine. We will have the capability to perform stereotactic treatments, and will be able to have more accurate collimation. Having a Calypso device in the vault with the new machine will allow us to incorporate the benefits of the new machine for our Calypso patients. For example, we could consider using the Calypso device for stereotactic treatments (on protocol, once we designed such a protocol), and could also have even better control of our radiation for prostate cancer treatments (because of the finer collimator).

There continues to be a delay in getting Brooke Army Medical Center added as an additional site on this grant to support the Reduced PTV margins protocol. Although the additional site was approved by MAMC IRB it is being held up in the regulatory review at BAMC. Unfortunately, this is out of our hands but we continue to be optimistic that approval will be granted.

Insufficient time remaining: Our work continues to yield exciting results, and as such we have already presented three presentations at national meetings and have been selected to present two more. We also presented two oral presentations at Madigan Research Day. As a side-result of our research, we have discovered applications for this technology beyond prostate cancer and are now able to use electromagnetic beacon transponders in treating breast cancer as well. Continuing our work in breast cancer is an important step that fits one of the main goals of our award - developing a "Center of Excellence in Targeted Radiation Therapy." We also are very interested in pursuing the palliative radiotherapy trial to replace the liver cancer protocol as detailed in Task 7. We are very enthusiastic to expand our research in these different areas, while also advancing our important work in prostate cancer. The SOW was amended to reflect these changes. The revised SOW was approved via email June 2013 and we are pending receipt of the award modification incorporating this new SOW. We are grateful to be given the opportunity to carry-on our research and continue to offer service personnel and their families who suffer from these types of cancers, this state-of-the-art treatment and hope to be granted a no-cost 2 year extension to continue these endeavors.

Key Personnel Updates:

- MAJ Brownwyn Stall from BAMC was added as a Sub-Investigator on the Reduced PTV Margins protocol.

Key Research Accomplishments:

- Enrolled 22 subjects (consented 24) on the Reduced PTV Margins protocol
- Enrolled 8 subjects (consented 11) on the Immobilization protocol
- Enrolled 16 (consented 20) subjects on the Post-prostatectomy protocol
- Treated 46 non-study patients with Calypso (including prostate and breast).

- Developed a database of volumetric and dosimetric anatomical data correlated with patient quality of life outcomes for patients treated on the reduced PTV margins study.

- Developed a database of anatomical data describing quantitatively the morphology of the prostatic fossa measured on over 300 treatment-matched CT scans in post-prostatectomy patients receiving radiation therapy.

- Continued development of Madigan as a center of excellence in Targeted Radiation therapy, including continued success of our annual multidisciplinary educational conference/visiting professorship.

- Developed technical expertise in using Calypso surface beacons to track breathing motion in left-sided breast cancer, allowing sparing of the heart.

Reportable Outcomes:

Abstract title: "Dose to the Muscles of Fecal Continence During Radiation Therapy for Prostate Cancer Using Calypso Localization." Poster was presented at the ASCO/ASTRO/SUO Genitourinary Oncology Symposium in February 2012.

Abstract title: "Anorectal Angle is Associated With Bowel Toxicity One Month Following Radiation Therapy for Prostate Cancer." Poster was presented at the ASTRO/RSNA 2013 Cancer Imaging and Radiation Therapy Symposium.

Abstract title: "The use of electromagnetic transponder beacons to reduce planning target volume (PTV) margins in post-prostatectomy patients undergoing adjuvant or salvage radiation therapy." Poster was presented at the ASCO/ASTRO 2013 Genitourinary Cancers Symposium.

Two research assistants have been provided employment supported by this research grant. Their work on this project has been fundamental in collecting data for our current and future research.

Conclusion: The "Targeted Radiation Therapy for Cancer Initiative" has provided a framework for developing Madigan Radiation Oncology into a center of excellence for targeted radiation therapy. Now we see our research momentum increasing, particularly as our prospective studies begin to mature.

Our currently underway analysis of our new database of post-prostatectomy anatomical information in over 400 treatment fractions will allow an unprecedented look at the inter- and intra- fraction changes in morphology of the prostatic fossa. Our planned participation in RTOG 0938 will allow us to contribute our expertise with Calypso localization to the national research question regarding extreme hypofractionation in prostate cancer. The continued accrual to our reduced PTV margins protocol, and participation of BAMC in this protocol, will lead to important quality of life outcomes publications in prostate cancer.

The research and education opportunities afforded by this progress have not gone unnoticed. On our most recent abstract submission we have active collaboration with the Madigan Radiology Department; a collaboration which we hope will expand. We also were able to include members of the pathology department in our visiting professorship last year, included a substantial number of primary care providers in our visiting professorship this year, and hope to continue to develop research collaboration with these groups in the upcoming year.

As discussed in this report, we are moving toward exciting new areas of research, including use of Calypso beacons to track breathing motion in breast cancer patients and using targeted radiation therapy modalities to improve our decades-old methods for treating metastatic lesions in the palliative setting. In addition to these areas of investigation we also envision in the distant future developing expertise with Calypso beacons implanted in the lung and other sites.

We are working hard to conserve our grant money (including redistributing our budget to cover a two-year no-cost extension) and hope to be granted this extra time so that we are able to implement our envisioned breast and palliative protocols as well as continue enrollment on our existing prostate cancer protocols.

This is an exciting era for targeted radiation therapy. With the help of the Congressionally Directed Medical Research Program we plan to treat our patients – military servicemen and women and their families – with lifesaving technology at the forefront of our field for years to come.

References: N/A

Appendices: See attached abstracts

APPENDIX I

Abstract: Dose to the muscles of fecal continence during radiation therapy for prostate cancer.

INTRODUCTION AND OBJECTIVE: Radiation therapy for prostate cancer can lead to loss of fecal continence; our understanding of the dose-volume relationships of this late toxicity continues to develop. The external anal sphincter (EAS), internal anal sphincter (IAS), the puborectalis (PRM), the pubococcygeus (PCM), and the illiococcygeus (ICM) muscles all contribute to fecal continence. We developed a reproducible method for contouring these muscles and in this preliminary study evaluate whether decreased planning target volume (PTV) margins lead to potentially clinically significant decreases in dose to these muscles during definitive radiation therapy for prostate cancer.

METHODS: Muscles involved in fecal continence were contoured for 10 consecutive patients on a prospective study of reduced PTV margins for treating low-to-intermediate risk prostate cancer with intensity modulated radiation therapy (IMRT) using an electromagnetic localization system. IMRT plans to a prescribed dose of 7740 cGy were developed using 10mm PTV margins (5mm posteriorly), and compared with actual treatment IMRT plans using 3mm circumferential PTV margins. Decreases in dose were evaluated for statistical significance using an unpaired t-test.

RESULTS: Reducing PTV margins decreased the mean PTV volume from 176.2 ml to 91.9 ml. Mean doses to the EAS, IAS, and rectum (REC) decreased significantly; from 11.0 Gy to 4.1 Gy ($p=0.005$), from 30.5 Gy to 15.0 Gy ($p = 0.004$), and from 43.7 Gy to 35.6 Gy ($p=0.006$) respectively. Decrease in the mean dose to the PRM was nearly statistically significant, 48.7 Gy to 34.6 Gy ($p = 0.055$). Decreases in mean doses to the PCM and ICM were not statistically significant; from 61.9 Gy to 55.2 Gy ($p = 0.107$), and from 40.7 Gy to 34.8 Gy ($p = 0.176$), respectively.

CONCLUSIONS: Using electromagnetic tracking to reduce PTV margins leads to a significant decrease in dose to the muscles of fecal continence, with mean dose decreases in a range that may be clinically significant.

APPENDIX II

Abstract: Anorectal Angle is Associated With Bowel Toxicity One Month Following Radiation Therapy for Prostate Cancer

Title: Anorectal Angle is Associated With Bowel Toxicity One Month Following Radiation Therapy for Prostate Cancer

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Purpose/Objectives: Bowel toxicity following radiation therapy (XRT) for prostate cancer can cause a significant decrease in patient quality of life. Some of this toxicity - such as rectal bleeding - seems to relate directly to damage to the rectal wall, while other elements of bowel toxicity - such as urgency, frequency, or fecal leakage - may be related to anal canal geometry and musculature. The anorectal angle (ARA) and the volume of the puborectalis muscle (VPRM) - which assists in maintaining the anorectal angle - are two image-based measurements which are known to be related to the maintenance of fecal continence. Here we explore whether a large pre-treatment ARA or a small VPRM are associated with increased bowel toxicity following XRT.

Materials/Methods: We studied 10 consecutive patients with low-to-intermediate risk prostate cancer treated on a prospective study with definitive intensity-modulated radiation therapy (IMRT). All patients completed the EPIC quality of life questionnaire at the end of treatment, and at 1 and 4 months post-treatment. We used the patients' answers on the bowel section of these questionnaires to divide the patients into two groups: one with few side effects as reflected by a score within 10% of the most favorable score possible, and the other with more side effects as reflected by a lower score. The patients' VPRMs were measured by contouring on planning CT scans. The anorectal angle was measured on sagittal CT scan reconstructions as the angle between the line down the center of the long axis of the anal canal, and the line down the center of the long axis of the rectum immediately superior to the anal canal. Both the VPRM and the ARA measurements were then categorized as "small" or "large" using the mean as the dividing line. We used Fisher's exact test to evaluate for a significant association between ARA and bowel toxicity and between VPRM and bowel toxicity.

Results: EPIC bowel toxicity scores varied from a low of 56.7 to a high of 100, with a mean of 83.8 and standard deviation of 14.76. VPRM varied from 6.45cc to 15.87cc (std. dev. 3.13), and was not associated with bowel toxicity ($p = 1.000$ at all time points). ARA varied between 93.5 and 121.8 deg (std. dev. 9.69), and was correlated with bowel toxicity one month following completion of therapy ($p = 0.048$), but not at the end of XRT ($p = 1.000$) or at 4 months post-treatment ($p = 0.524$).

Conclusions: These results are hypothesis-generating and based on a very small sample size. Further evaluation of the association of ARA with bowel toxicity following XRT for prostate cancer in a larger cohort is warranted. If there is an association between baseline ARA and bowel toxicity, measuring the ARA on a pre-treatment CT scan could allow more informed counseling of patients regarding the risks for bowel toxicity following XRT.

APPENDIX III

Abstract: The use of electromagnetic transponder beacons to reduce planning target volume (PTV) margins in post-prostatectomy patients undergoing adjuvant or salvage radiation therapy

Background: We determined necessary PTV margins when beacons are used to localize the prostatic fossa in post-prostatectomy patients. We hypothesized beacon localization would allow for decreased PTV margins and increased normal tissue sparing.

Methods: 10 patients requiring post-prostatectomy radiation were treated on this IRB-approved prospective study. Each patient had 3 beacons placed in the prostatic fossa. Daily radiation was localized by beacons and a cone-beam CT (CBCT) taken for analysis. By measuring differences between the treated clinical target volume (CTV) and relevant anatomy on 5 equally-spaced axial CT slices we calculated necessary PTV margins for each fraction. We then auto-fused each CBCT scan with the treatment planning scan, recorded the shifts incurred, and repeated our measurements, representing a hypothetical CBCT - localized treatment. We report a PTV margin for each technique that would cover the CTV during 90% of all 304 fractions analyzed. We also used intra-fraction motion data to produce a worst-case estimate of required PTV bladder margins.

Results: The average shifts from the beacon to CBCT- localized isocenter were 2.9, 3.2, 1.0 mm and 0.58 degrees in the vertical, longitudinal, lateral, and rotational planes, respectively. Necessary PTV margins for beacon and CBCT localization are listed in Table 1.

Conclusions: Beacon localization "attaches" the CTV to the bladder, allowing a decrease in PTV margin or the amount of posterior bladder included in the CTV. This could lead to decreased rates of bladder toxicity.

Table 1: Necessary PTV margins based on 90th percentile of 304 fractions analyzed

					Necessary PTV margins				
Axial CT slice location and reference structure	**Direction**				**Without intra-fraction motion**			**With intra-fraction motion**	
	ANT	POST	LT	RT	BEACONS (mm)	CBCT (mm)		BEACONS (mm)	CBCT (mm)
INFERIOR									
Symphysis pubis	X				3	6			
Ant rectal wall		X			9	7			

INFERIOR-MID									
Symphysis pubis	X				3	6			
Ant rectal wall		X			7	5			
MIDDLE									
Symphysis pubis	X				3	6			
Ant rectal wall		X			5	3			
Left obt internus			X		4	4			
Right obt internus				X	5	3			
SUPERIOR-MID									
Post bladder wall	X				7	12		8	13
Ant rectal wall		X			7	2			
SUPERIOR									
Post bladder wall	X				8	15		8	15
Ant rectal wall		X			9	6			